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Breast Cancer

Subtype-Guided ^{18}F-FDG PET/CT in Tailoring Axillary Surgery Among Patients with Node-Positive Breast Cancer Treated with Neoadjuvant Chemotherapy: A Feasibility Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Subtype-guided • ^{18}[F]-fluorodeoxyglucose positron emission tomography/computed tomography • Response • Axillary surgery • Neoadjuvant chemotherapy

Abstract

Background. The purpose of this study was to investigate the value of ^{18}[F]-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) in tailoring axillary surgery by predicting nodal response among patients with node-positive breast cancer after neoadjuvant chemotherapy (NAC).

Methods. One hundred thirty-three patients with breast cancer with biopsy-confirmed nodal metastasis were prospectively enrolled. ^{18}F-FDG PET/CT scan was performed before NAC (a second one after two cycles with baseline maximum standardized uptake value [SUV_{max}] ≥2.5), and a subset of patients underwent targeted axillary dissection (TAD). All the patients underwent axillary lymph node dissection (ALND). The accuracy was calculated by a comparison with the final pathologic results.

Results. With the cutoff value of 2.5 for baseline SUV_{max} and 78.4% for change in SUV_{max}, sequential ^{18}F-FDG PET/CT scans demonstrated a sensitivity of 79.0% and specificity of 71.4% in predicting axillary pathologic complete response with an area under curve (AUC) of 0.75 (95% confidence interval, 0.65–0.84). Explorative subgroup analyses indicated little value for estrogen receptor (ER)-negative, human epidermal growth factor receptor 2 (HER2)-positive patients (AUC, 0.55; sensitivity, 56.5%; specificity, 50.0%). Application of ^{18}F-FDG PET/CT could spare 19 patients from supplementary ALNDs and reduce one of three false-negative cases in TAD among the remaining patients without ER-negative/HER2-positive subtype.

Conclusion. Application of the subtype-guided ^{18}F-FDG PET/CT could accurately predict nodal response and aid in tailoring axillary surgery among patients with node-positive breast cancer after NAC, which includes identifying candidates appropriate for TAD or directly proceeding to ALND. This approach might help to avoid false-negative events in TAD.

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Implications for Practice: This feasibility study showed that ^{18}[F]-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) could accurately predict nodal response after neoadjuvant chemotherapy (NAC) among patients with breast cancer with initial nodal metastasis except in estrogen receptor-negative, human epidermal growth factor receptor 2-positive subtype. Furthermore, the incorporation of ^{18}F-FDG PET/CT can tailor subsequent axillary surgery by identifying patients with residual nodal disease, thus sparing those patients supplementary axillary lymph node dissection. Finally, we have proposed a possibly feasible flowchart involving ^{18}F-FDG PET/CT that might be applied in post-NAC axillary evaluation.

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Introduction

Effective chemotherapy regimens, radiation therapy, and targeted and endocrine therapies have inspired the evolution of the breast cancer operational model to become less radical [1, 2]. Preoperative treatment has been increasing in a significant manner during the past decade and has improved the operable rate, breast-conserving rate, and the rate of axillary pathologic complete response (Ax-pCR) [3]. In the era of individualized medicine, selective neoadjuvant chemotherapy (NAC) regimens performed in patients with chemoresponsive breast cancer lead to an approximately 40% conversion rate from node positive to node negative [4]. In some studies, the rate of Ax-pCR was reported to be as high as 80% in human epidermal factor growth receptor 2 (HER2)-positive patients treated with trastuzumab [5–7]. However, much controversy remained for the assessment of axillary lymph node (ALN) status after NAC among patients with initial nodal metastasis [8].

Pooled data have shown great variability in the false-negative rate (FNR) of sentinel lymph node (SLN) biopsy among patients who have underwent NAC, with a suboptimal FNR of 12% [9]. A remarkably low FNR of 2.0% was achieved among patients who were initially node-positive in a study via a novel surgical technique termed targeted axillary dissection (TAD) [10]. In addition, a clinical trial conducted by Classe et al. concluded that a low FNR was related to a better response to neoadjuvant treatment at the tumor site or the nodes [11]. Intuitively, preoperative identification of patients with breast cancer with a high rate of Ax-pCR or residual disease in axilla would allow for tailoring surgical planning for a less-invasive procedure such as a TAD or a direct completion axillary lymph node dissection (ALND), thus reducing unnecessary procedures or expense as well as the false-negative cases. Correspondingly, Caudle et al. found that fine-needle aspiration of the clipped lymph node could not reliably identify residual nodal disease after NAC with a high false-negative rate [12]. Furthermore, two studies consistently demonstrated that the extremely low nodal positivity was achieved among patients with concurrent HER2-positive or triple-negative breast cancer and breast pathologic complete response (pCR), which might enable the omission of axillary surgery in this subset of patients [5, 13].

In recent years, ^{18}[F]-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) has shown considerable ability to early assess response to NAC by monitoring the change of a tumor's maximum standardized uptake value (SUV_{max}) value under therapy, which may also result in the cessation of inefficient chemotherapy and allow for refinement of treatment [14, 15].

Therefore, we sought to evaluate whether ^{18}F-FDG PET/CT could serve as a tool in tailoring axillary surgery including TAD or ALND after NAC. We aimed to develop a possible flowchart combining ^{18}F-FDG PET/CT and TAD, which may be applied in post-NAC axillary evaluation in the future.

Subjects, Materials, and Methods

Patients

This feasibility study recruited patients aged 18 to 70 years with invasive breast cancer who presented with histologically confirmed nodal metastasis and planned to undergo NAC (with or without targeted therapy) at the Fudan University Shanghai Cancer Center (FUSCC) from 2014 to 2018. This study was approved by the Institutional Ethics Committee of FUSCC. Signed informed consent was obtained from every patient prior to participation in this study. Figure 1 illustrates the study flow. Patients with advanced breast cancer or diabetes and those who underwent prior surgery or radiation therapy on ipsilateral axillary lymph nodes were ineligible for this study. Pregnant or nursing women were also excluded from this study.

Receptor Status Determination

The hormone receptor, HER2, and Ki67 values were determined by immunohistochemistry (IHC) of the primary tumor in hematoxylin and eosin (H&E)–stained sections obtained from core needle biopsies. The cutoff values for estrogen receptor (ER) positivity and progestogen receptor positivity were established at 10% of tumor cells with positive nuclear staining. The HER2 status was considered positive if the IHC score was 3+ or if an IHC score of 2+ was confirmed by fluorescence in situ hybridization (FISH). We followed the criterion that a HER2 copy number greater than 6.0 or a HER2/CEP17 (chromosome enumeration probe 17) ratio greater that 2.0 was defined as FISH-positive [16].

Neoadjuvant Chemotherapy

The NAC agents were administered according to the National Comprehensive Cancer Network guidelines and clinical trial results regarding NAC in our center; moreover, the effectiveness of the regimen had to be demonstrated [17]. All enrolled patients received four to eight cycles of NAC. Trastuzumab was added to the NAC regimen among all the women with HER2-positive breast cancer. Neoadjuvant treatment regimens included anthracycline/taxanes (±trastuzumab), carboplatin/paclitaxel (±trastuzumab) and docetaxel/trastuzumab (±pertuzumab).

^{18}F-FDG PET/CT Imaging

^{18}F-FDG was produced by cyclotron (CTI RDS Eclipse ST; Siemens, Munich, Germany) and by using Explora Synthesis FDG4 modules at our center. All eligible patients were required to fast for at least 6 hours to ensure glucose blood levels below 10 mmol/L (180 mg/dL), which was a prerequisite for undergoing the procedure. Scanning was initiated 1 hour after administration of the tracer (7.4 MBq/kg or 0.2 mCi/kg). The baseline ^{18}F-FDG PET/CT scans were scheduled prior to initiation of the neoadjuvant therapy and at least 10 days after the core biopsy. In our study, 2.5 was set as a suitable baseline SUV_{max} cutoff value in the axilla for monitoring axillary metastasis, according to previous studies [18]. Therefore, the second scan was scheduled after completing the second cycle of neoadjuvant therapy if the baseline axillary SUV_{max} was ≥2.5 (7-day window). The same acquisition parameters were used for baseline and second PET/CT scans. All the PET examinations of the patients were performed at the same center with the same equipment and method. The data from the ^{18}F-FDG PET/CT

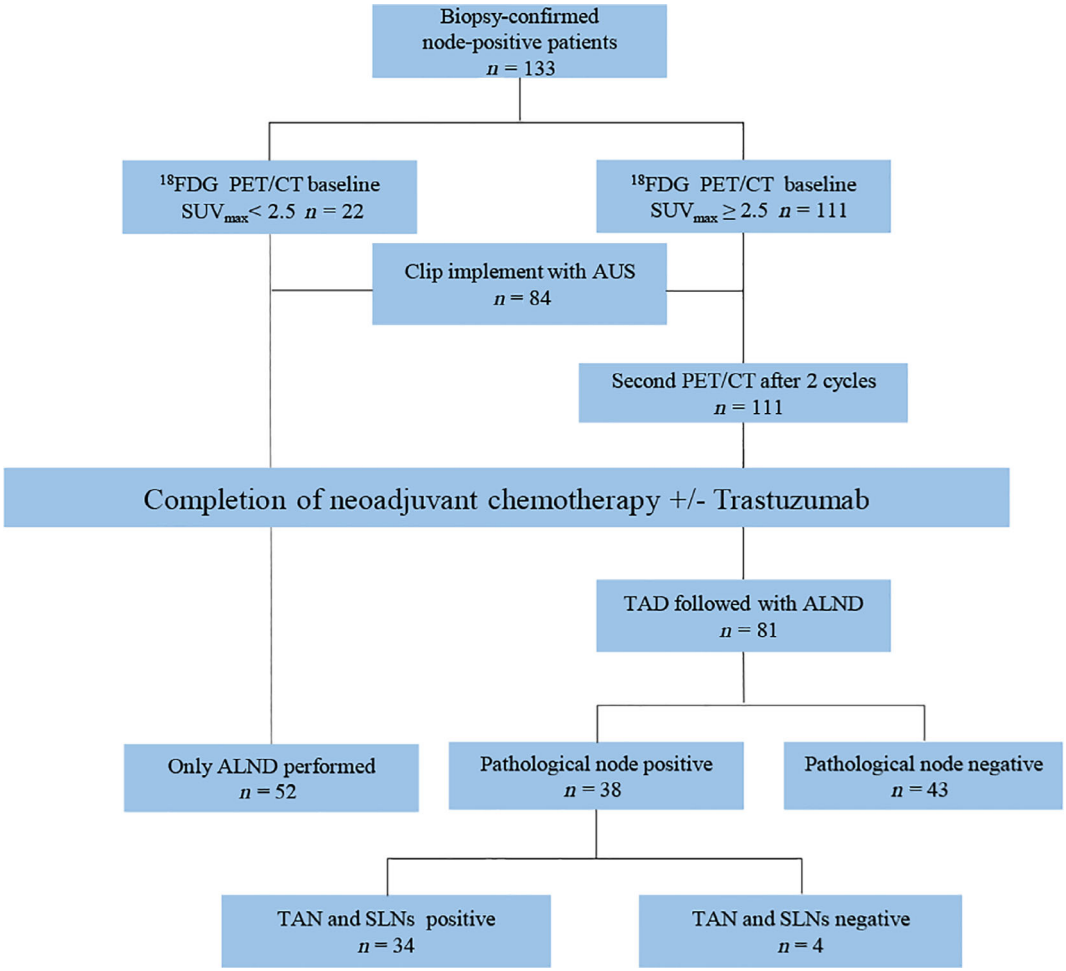

Figure 1. Flow of this study.
Abbreviations: ^{18}FDG, ^{18}[F]-fluorodeoxyglucose; ALND, axillary lymph node dissection; AUS, axillary ultrasound; PET/CT, positron emission tomography/computed tomography; SLN, sentinel lymph node; SUV_{max}, maximum standardized uptake value; TAD, targeted axillary dissection; TAN, targeted node.

examinations were interpreted by two nuclear medicine radiologists who were blinded to the clinical, radiologic, and pathologic findings. All images were analyzed on a clinical Leonardo workstation with TrueD software. All the axillary lymph nodes with abnormal ^{18}F-FDG uptake were calculated manually, and the hottest one was selected, with its SUV_{max} being defined as the SUV_{max} of the baseline ^{18}F-FDG PET/CT (SUV_{max1}). In the second PET/CT scan, the same axillary lymph node was targeted, and its SUV_{max} was defined as the SUV_{max} of the second ^{18}F-FDG PET/CT. The absolute value of the relative changes in the SUV_{max} between two ^{18}F-FDG PET/CTs (ΔSUV_{max}) was calculated according to the following formula:

$$\Delta SUV_{max} = \left[\left(SUV_{max}\ \text{of second}\ ^{18}\text{F-FDG PET/CT} - SUV_{max}\ \text{of baseline}\ ^{18}\text{F-FDG PET/CT}\right)/ SUV_{max}\ \text{of baseline}\ ^{18}\text{F-FDG PET/CT}\right] \times 100\%.$$

(All calculated ΔSUV_{max} values were set and presented as absolute values in our study). Notably, a decrease in SUV_{max} is deemed a positive response to NAC.

TAD Procedures and Pathological Evaluation

Following reports of the findings from the ACOSOG Z1071 trial and subsequent recommendations with respect to the National Comprehensive Cancer Network guidelines, we began to implant a clip into positive lymph nodes verified by fine-needle aspiration under the guidance of ultrasound after enrolment of some participants (clinical T1–3N1M0 prior to NAC) [19]. If a biopsied node was cytologically or pathologically proven positive, node clipping was conducted within 3 days, and a PET/CT scan was subsequently performed within 7 days of the clipping. The details of the TAD procedure were described in a previous study published by our center [20]. Dual mapping agents including radiolabeled colloid and blue dye were adopted to detect SLNs during operation. Here, we defined clipped nodes as targeted nodes (TANs). Detected SLNs and TANs were obtained and submitted as TAD specimens for pathologic evaluation. All the TANs were serially sectioned and processed in a method similar to that of the detected SLNs. Formalin-fixed paraffin-embedded tissue blocks were sectioned in 5-micron-thick sections and stained with H&E for evaluation by breast pathologists. Any metastatic foci, including isolated tumor cells (ITCs) and micrometastases, were considered node-positive. All the

patients underwent ALNDs to determine final pathologic results.

Statistical Analysis

Receiver operating characteristics (ROCs) and areas under curves (AUCs) were employed to evaluate the predictive value of ^{18}F-FDG PET/CT by determining the optimum cutoff for ΔSUV_{max}. Statistical analysis was calculated among patients who underwent two successive ^{18}F-FDG PET/CT scans. Logistic regression analysis was used to determine independent factors predictive of Ax-pCR. For categorical variables, the difference was calculated by the chi-squared test or Fisher's exact tests when necessary. Statistical analysis was performed with IBM SPSS 20.0 software (SPSS Inc., Chicago, IL), and *p* values were reported as two-sided with an alpha of .05.

Results

Baseline Clinicopathological Characteristics of Patients

Overall, 133 eligible patients were enrolled in our study. The clinicopathological characteristics of these patients categorized by SUV_{max1} are shown in Table 1. All the patients had a baseline ^{18}F-FDG PET/CT before NAC. A total of 68 patients were observed to have no residual foci in the axillary lymph nodes after NAC, with an Ax-pCR rate of 51.1%. The Ax-pCR rates of the four subtypes based on ER and HER2 status were 15.8% (6/38) in the ER-positive/HER2-negative subtype, 56.3% (18/32) in the ER-negative/HER2-negative subtype, 63.0% (17/27) in the ER-positive/HER2-positive subtype, and 75.0% (27/36) in the ER-negative/HER2-positive subtype. Furthermore, 111 and 84 patients underwent two consecutive ^{18}F-FDG PET/CT scans and clip placement before the complement of NAC, respectively.

Baseline and Change in SUV_{max} and Correlation with Axillary Response to NAC

Among 111 patients undergoing two consecutive ^{18}F-FDG PET/CTs, baseline SUV_{max1} was not significantly associated with Ax-pCR. ROC analysis of baseline SUV_{max1} yielded an AUC of 0.55 (95% confidence interval [CI], 0.45–0.66). A significant difference was observed in median SUV_{max} at second cycle as well as percentage reduction in SUV_{max} between patients who obtained Ax-pCR versus those who did not; however, ROC analysis with SUV_{max} after second cycle as the predictor yielded an AUC of 0.71 (95% CI, 0.61–0.81; supplemental online Fig. 1).

With an optimum cutoff value of 78.4% (supplemental online Table 1 and representative images shown in supplemental online Fig. 2), the AUC of the ΔSUV_{max} (n = 111) had a maximum area of 0.75 (95% CI, 0.65–0.84), with a sensitivity of 79.0%, a specificity of 71.4%, a positive predictive value (PPV) of 77.8%, and a negative predictive value (NPV) of 72.9% (Table 2 and Fig. 2). We deemed SUV_{max1} ≥2.5 and ΔSUV_{max} ≥78.4% to be a clinicopathologic factor for PET/CT. Univariate analysis revealed that this factor, ER, HER2 status, and Ki67 value were independent factors significantly associated with Ax-pCR. Furthermore, multivariate logistic analyses also indicated that PET/CT factor (odds ratio [OR], 8.80; 95% CI, 3.59–21.61), ER (OR, 0.25; 95% CI, 0.10–0.62), and HER2 (OR, 3.75; 95% CI, 1.55–9.09) were three independent factors significantly associated with Ax-pCR after NAC (p < .05; Table 3).

Table 1. Clinicopathologic characteristics of patients

Characteristics	SUV_{max1} <2.5 (n = 22), n (%)	SUV_{max1} ≥2.5 (n = 111), n (%)
Age, median (range), years	43 (28–60)	49 (26–68)
Menstrual status		
Premenopausal	17 (77.2)	63 (56.8)
Postmenopausal	5 (22.8)	48 (43.2)
Clinical T stage		
T0	0 (0)	4 (3.6)
T1	4 (18.2)	11 (9.9)
T2	16 (72.7)	73 (65.8)
T3	2 (9.1)	23 (20.7)
Clinical N stage		
N1	20 (90.9)	84 (75.7)
N2	2 (9.1)	25 (22.5)
N3	0 (0)	2 (1.8)
Progestrogen receptor		
Positive	15 (68.2)	41 (36.9)
Negative	7 (31.8)	70 (63.1)
Tumor receptor subtype		
ER+/HER2−	11 (50.0)	27 (24.3)
ER+/HER2+	4 (18.2)	23 (20.7)
ER−/HER2+	5 (22.7)	31 (27.9)
ER−/HER2−	2 (9.1)	30 (27.1)
Ki67		
<20%	4 (18.2)	9 (8.1)
≥20%	18 (81.8)	102 (91.9)
Type of breast surgery		
Lumpectomy	8 (36.4)	24 (21.6)
Mastectomy	14 (63.6)	87 (78.4)
Type of axillary surgery		
TAD plus ALND	14 (63.6)	67 (60.4)
ALND alone	8 (36.4)	44 (39.6)
Axillary pCR		
Yes	6 (27.3)	62 (55.9)
No	16 (72.7)	49 (44.1)

Abbreviations: ALND, axillary lymph node dissection; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; pCR, pathologic complete response; SUV_{max1}, maximum standardized uptake value at baseline; TAD, targeted axillary dissection.

Exploratory Subgroup Analysis Based on ER and HER2 Status

Based on the ER and HER2 status, an exploratory subgroup analysis was performed among four subtypes (supplemental online Fig. 3). Interestingly, the ROC curve showed that for the ER-negative/HER2-positive subtype with the highest Ax-pCR

Table 2. Accuracy of ^{18}[F]-fluorodeoxyglucose positron emission tomography/computed tomography to predict Ax-pCR in overall population and different subtypes

Characteristics	Entire cohort	ER-negative, HER2-positive subtype	Other subtypes
No. of patients	111	31	80
Ax-pCR rate, %	55.9	74.2	48.8
AUC (95% CI)	0.75 (0.65–0.84)	0.55 (0.31–0.79)	0.80 (0.70–0.91)
p value	<.05	.69	<.05
Optimum cutoff, %	78.4	79.9	76.2
Accuracy, %	75.7	54.8	77.5
Sensitivity, %	79.0	56.5	84.6
Specificity, %	71.4	50.0	70.7
PPV, %	77.8	76.5	73.3
NPV, %	72.9	28.6	82.9

Abbreviations: AUC, area under curve; Ax-pCR, axillary pathologic complete response; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NPV, negative predictive value; PPV, positive predictive value.

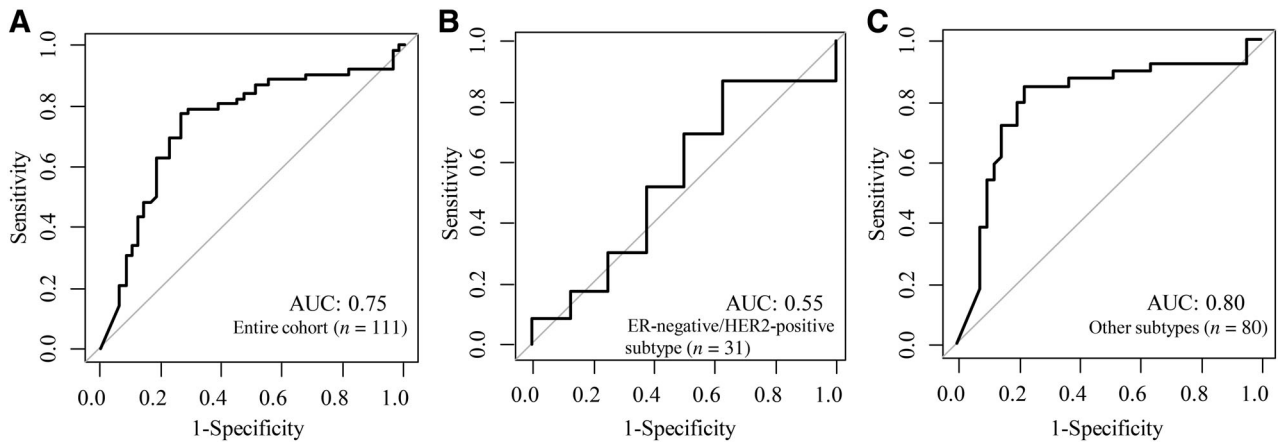

Figure 2. Receiver operating characteristic curve for the change in maximum standardized uptake values in the prediction of axillary pathological complete response after neoadjuvant therapy. **(A):** Among entire population. **(B):** ER-negative/HER2-positive. **(C):** Other subtypes.
Abbreviations: AUC, area under curve; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

rate among four subtypes, serial ^{18}F-FDG PET/CTs showed an unsatisfactory performance (AUC, 0.55; 95% CI, 0.31–0.79) with an unacceptably low sensitivity (56.5%), specificity (50.0%), and NPV (28.6%; Table 3 and Fig. 2). When ER-negative/HER2-positive cases were excluded, patients could be classified as two cohorts of high and low Ax-pCR rate, respectively. The difference between these two cohorts had indeed reached a statistical significance (Ax-pCR rate, 76.7% vs. 16.7%; $p < .01$; supplemental online Table 2). Excluding ER-negative/HER2-positive subtype, the ROC analysis of ΔSUV_{max} yielded an AUC of 0.80 (95% CI, 0.70–0.91) among the remaining subtypes (Table 3 and Fig. 2). Compared with other cut points examined, including the cutoff value of 76.2% determined on the basis of Youden's index, the threshold of 75.0% is considered clinically optimal for its high NPV (83.3%) for non–Ax-pCR (supplemental online Table 3).

A Combination of ^{18}F-FDG PET/CT and TAD in Patients Without ER-Negative/HER2-Positive Subtype

Overall, a total of 81 patients successfully received TAD. Excluding the 20 ER-negative/HER2-positive patients, 61 patients with other subtypes successfully underwent TAD. 47.5% (29/61) of patients present with positive SLNs or TANs might have undergone supplementary ALNDs after TAD (Fig. 3), with six cases presenting with only ITCs or micrometastases. If the TAD criteria of an SUV_{max1} ≥2.5 and a ΔSUV_{max} ≥75.0% was adopted for ^{18}F-FDG PET/CT scans according to supplemental online Figure 4 (a proposed algorithm based on our findings), 19 supplementary ALNDs would have been avoided in 22 patients with SUV_{max1} <2.5 or ΔSUV_{max} <75.0%; subsequently, only 16.4% (10/61) of the patients should have undergone TADs followed by supplementary ALNDs to eradicate the remaining disease with a median of only one pathologically positive ALN (ranging from one to four positive nodes; Fig. 3). This difference was statistically significant ($p < .05$). In addition, only two cases went directly to ALND based on ^{18}F-FDG PET/CT but were found to have an Ax-pCR. Notably, one of three false-negative events could have been avoided with the use of ^{18}F-FDG PET/CT in patients without ER-negative/HER2-positive subtypes (Fig. 3).

Table 3. Univariate and multivariate analysis for the factors of axillary pathologic complete response

	Univariate		Multivariate	
Factors	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Age, years				
<40	1.0		1.0	
≥40	0.81 (0.36–1.86)	.62	0.47 (0.16–1.36)	.16
Clinical T stage				
0–1	1.0		1.0	
2	0.57 (0.21–1.58)	.28	0.62 (0.17–2.24)	.47
3	0.54 (0.16–1.82)	.32	0.25 (0.05–1.26)	.09
Clinical N stage				
1	1.0		1.0	
2–3	1.03 (0.45–2.35)	.94	1.26 (0.37–4.28)	.71
ER				
Negative	1.0		1.0	
Positive	0.28 (0.14–0.57)	<.05	0.25 (0.10–0.62)	<.05
HER2				
Negative	1.0		1.0	
Positive	4.44 (2.14–9.21)	<.05	3.75 (1.55–9.09)	<.05
Ki67				
<20%	1.0		1.0	
≥20%	6.72 (1.43–31.64)	<.05	7.48 (0.95–59.03)	.06
Chemotherapy cycles				
4	1.0		1.0	
5–6	2.09 (0.93–4.72)	.08	1.17 (0.28–4.80)	.83
7–8	0.59 (0.24–1.43)	.24	2.61 (0.37–18.27)	.33
Chemotherapy regimen				
Anthracycline/taxanes (±T)	1.0		1.0	
Carboplatin/paclitaxel (±T)	7.73 (2.71–22.09)	<.05	3.23 (0.75–13.93)	.83
Docetaxel/T (±P)	4.80 (1.00–23.07)	.05	2.69 (0.30–23.97)	.38
^{18}F-FDG PET/CT				
SUV_{max1} <2.5 or ΔSUV_{max} <78.4%	1.0		1.0	
SUV_{max1} ≥2.5 and ΔSUV_{max} ≥78.4%	9.40 (4.25–20.78)	<.05	8.80 (3.59–21.61)	<.05

Abbreviations: ΔSUV_{max}, change in maximum standardized uptake values; ^{18}F-FDG PET/CT, ^{18}[F]-fluorodeoxyglucose positron emission tomography/computed tomography; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; P, pertuzumab; SUV_{max1}, maximum standardized uptake value at baseline; T, trastuzumab.

Discussion

To the best of our knowledge, the current study is the first to demonstrate the feasibility of the ^{18}F-FDG PET/CT application for tailoring axillary surgery by selecting optimal population for TAD or ALND. This approach could be used to directly decrease the number of supplementary ALNDs and false-negative events.

The ability to capture dynamic metabolic change makes ^{18}F-FDG PET/CT a powerful tool for monitoring the response of breast cancer under the pressure of a neoadjuvant treatment [14]. Specifically, Koolen et al. reported that the relative decrease in the SUV_{max} was significantly higher in patients with Ax-pCR than in those without and that a relative decrease of more than 60% in the SUV_{max} on ^{18}F-FDG PET/CT after two cycles of NAC could better predict Ax-pCR [21]. Of note, the findings of this study agreed with ours, but the cutoff of 78.4% in our study might be higher than that in Koolen's study. Furthermore, Rousseau's study confirmed the ability of ^{18}F-FDG PET/CT to monitor the axillary response during NAC [18]. However, they concluded that when a cutoff of a decrease of 50% after the first cycle of treatment was adopted, ^{18}F-FDG PET/CT could accurately predict nodal response. We speculated that this was largely attributable to heterogeneity concerning treatment approaches such as various chemotherapeutic agents and possibly targeted treatments [22]. In our study, patients with weak ^{18}F-FDG uptake (SUV_{max1} <2.5) were excluded, most of whom were ER-positive and HER2-negative. These patients indeed demonstrated a lower response to NAC and Ax-pCR rate, which was also consistent with other studies [3].

Additionally, multivariate analysis confirmed that SUV_{max1} ≥2.5 and ΔSUV_{max} ≥78.4% was independently and

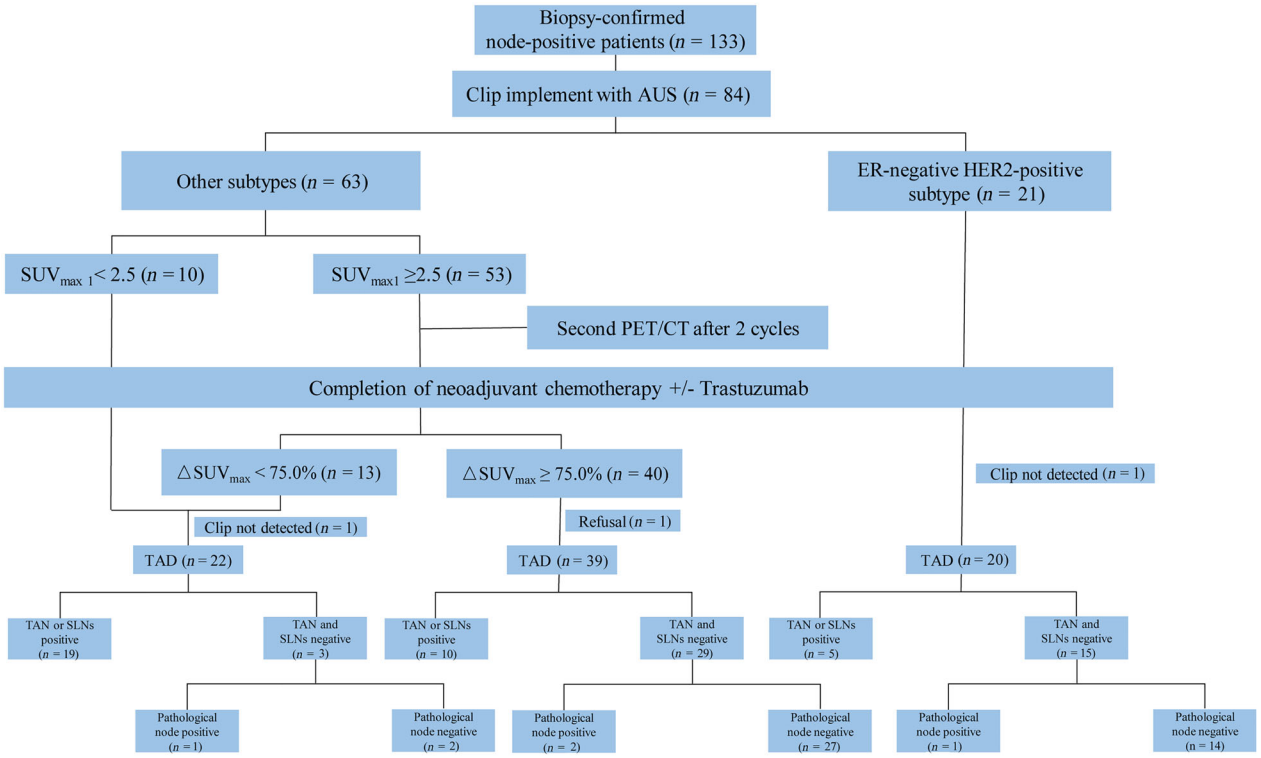

Figure 3. Subtype-guided application combining ^{18}[F]-fluorodeoxyglucose PET/CT and TAD in the current study.
Abbreviations: ΔSUV_{max}, change in maximum standardized uptake values; AUS, axillary ultrasound; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PET/CT, positron emission tomography/computed tomography; SLN, sentinel lymph node; SUV_{max1}, maximum standardized uptake value at baseline; TAD, targeted axillary dissection; TAN, targeted node.

significantly associated with Ax-pCR. ER negativity as well as HER2 positivity could also serve as predictive factors for Ax-pCR. Similarly, many studies have consistently reported that the highest rate of Ax-pCR could be achieved in the ER-negative/HER2-positive subtype, reaching an Ax-pCR rate of more than 80% [6, 7].

Interestingly enough, in the current study, a low NPV of 28.6% for sequential ^{18}F-FDG PET/CT was noted in ER-negative/HER2-positive patients, indicating extremely poor ability to determine nodal response for NAC. Furthermore, the Ax-pCR rate (74.2%) was close to the PPV (76.5%) rate for this subtype, indicating little value in screening these patients. Likewise, our findings on the predictive value of ΔSUV_{max} confirm and extend the findings from the previous reports [23, 24]. However, three studies had produced somewhat contradictory conclusions that ^{18}F-FDG PET/CT during NAC was suitable for the predicting treatment response in patients with HER2-positive breast cancer [25–27]. Difference in study design (second PET/CT scan after first or second cycle), definitions in endpoint (pCR in breast, axilla or both), and mixture of HER2-positive breast cancer regardless of ER status might result in these conclusions.

In recent years, it has been established that the improvements in surgical techniques could help render an acceptable FNR of less than 10% [19, 28]. Caudle et al. demonstrated the feasibility of TAD in their report with an FNR of 2% [10]. In this context, applying ^{18}F-FDG PET/CT to identify patients with breast cancer with pCR or residual disease in axilla will allow for further tailoring axillary surgery by reducing unnecessary procedures and expense required for TADs. Indeed, incorporation of this approach to TAD could have significantly reduced 19 second ALNDs and one of three false-negative cases in TADs among patients without ER-negative/HER2-positive subtype.

This study was limited to a single institution and sample size; the result deserves further investigation in a larger population. Additionally, heterogeneity in NAC might result in bias, as changes in tumor glucose metabolism is dependent on both the number of NAC cycles and the regimens used. Of note, as shown in Figure 3, nine cases not meeting the criteria of $SUV_{max1} \geq 2.5$ and $\Delta SUV_{max} \geq 75.0\%$ ultimately obtained Ax-pCR among patients without ER-negative/HER2-positive subtype, indicating that directly performing ALND would have been overtreatment in these cases. Following the findings from our study, we have designed a possibly feasible algorithm used for post-NAC axillary evaluation based on both ^{18}F-FDG PET/CT and TAD, as shown in supplemental online Figure 4.

Conclusion

Early assessment by ^{18}F-FDG PET/CT could accurately predict axillary response and could help to tailor subsequent axillary surgery after NAC among patients with breast cancer with biopsy-proven axillary metastasis.

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Disclosures

The authors indicated no financial relationships.

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